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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/631,883	07/31/2003	Daniel Kahne	PUAM-0257	1801

23377 7590 04/09/2007

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EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1639	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/631,883	KAHNE ET AL.	
	Examiner	Art Unit	
	Jeff Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,26,27,102,103,105-107,116 and 117* is/are pending in the application.

4a) Of the above claim(s) *117* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 5, 6, 26, 27, 102, 103, 105-107 and 116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1, 5, 6, 26, 27, 102, 103, 105-107, 116 and 117, are pending in the instant Application; claim 117 is withdrawn as being directed to a non-elected invention (*i.e.*, glucose residue, not the disaccharide); claims 1, 5, 6, 26, 27, 102, 103, 105-107 and 116 are the subject of the Office Action below.

Claim Rejections - 35 USC § 102 - Withdrawn

The rejection of claims 1, 5, 6, 26, 27, 102, 103, 105-107 and 116, are rejected under 35 U.S.C. 102(b) as being anticipated by Higgins et al., U.S. Patent No. 4,548,925, issued October 22, 1985, is withdrawn.

New and Maintained Rejections

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5, 6, 26, 27, 102, 103, 105-107 and 116, are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5, 6, 26, 27, 102, 103, 105-107 and 116, are indefinite because it is not clear how the disaccharide group is attached to the vancomycin heptapeptide, and whether A4 corresponds to the chemical structure of natural vancomycin (*i.e.*, the sequence of SEQ ID NO:1 does not require A4 to be the naturally occurring vancomycin amino acid structure). Correction is required.

Claim Rejections - 35 USC § 112, first paragraph (Scope of Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

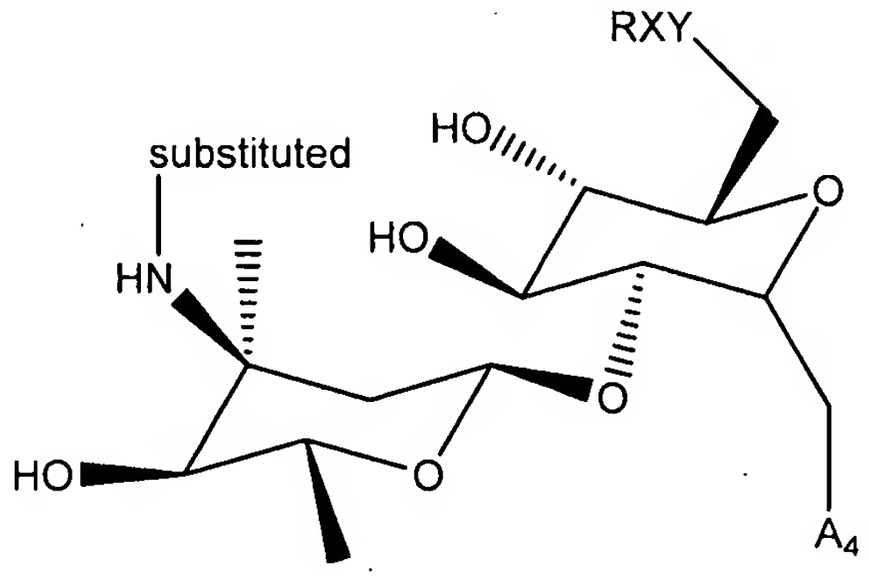
pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1, 5, 6, 26, 27, 102, 103, 105-107 and 116 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in a determination of undue experimentation are disclosed in *In re Wands* (USPQ 2d 1400: CAFC 1988) which include: a) The breadth of the claims; b) the nature of the invention; c) the state of the prior art; d) the level of one of ordinary skill; e) The level of predictability in the art; f) The amount of direction provided by the inventor; g) The presence or absence of working examples; and h) the quantity of experimentation necessary needed to make or use the invention based on the disclosure; See :In re Wands USPQ 2d 1400 (CAFC 1988).

The breadth of the claims

The breadth of potential glycopeptides of different chemical structure as encompassed by claims 1 and 102 is unsupported in light of the failure to substantially teach compounds as broadly as claimed. Specifically, although Applicants have shown support for the heptapeptide structure of naturally occurring vancomycin, Applicants have not shown support beyond the disaccharide structural feature of the following formula:



wherein A_4 is the attachment site of the disaccharide for naturally occurring vancomycin, and Y is attached at the C6.

The nature of the Invention/State of the Prior art

The present invention is directed to the making and screening of glycopeptide antibiotics; although it is noted that claims 1 and 102 are not so limited. Additionally, it is noted that "the nature and placement of the sugars on the glycopeptide antibiotics play critical roles in antibiotic activity". In this regard it is further noted that, "that there have been no reports of modification on the glucose residues of vancomycin which have affected activity" E.g. see specification page 7, first full paragraph.

The level of one of ordinary skill

The level of one of ordinary skill in the art is high, and would likely encompass a person having earned a MS or Ph.D. with at least a few years experience following their degree.

The level of predictability in the art

The sugar residues of the vancomycin and other glycopeptide antibiotics have been shown to affect binding activities e.g. "the nature and placement of the sugars on the glycopeptide antibiotics play critical roles in antibiotic activity". Additionally, structural changes in the sugar residues can produce significant changes in antibiotic activity. See *e.g.* specification page 4, first full paragraph. Accordingly, the making and potential usefulness of "glycopeptide" compounds of different chemical structure is not a priori predictable. Courts have recognized that reaction steps or compound structure which is shown to be (e.g. by applicant or prior art) to be critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See In re Mayhew, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976); Ex parte Bhide (BdPatApp&Int) 42 USPQ2d 14.

For example, on pages 970-972, Pace (Pace *et al.*, *Biochemcial Pharmacology 71*:968-980 (**2006**)) shows how even the smaller class of vancomycin compounds have unpredictable activities, let alone the largely diverse claimed core by Applicants:

> "The goal of the project that culminated in the discovery of oritavancin was to improve over vancomycin's pharmacokinetic properties, and was based on an understanding of the relevant structure–activity relationship differences between vancomycin and teicoplanin. Improvements in alkylated and acylated analogs of vancomycin were deemed inadequate,

> and other natural product glycopeptides were subsequently evaluated as platforms [108–111]. Compounds like chloreremomycin (LY264826) exhibiting better activity and spectrum were utilized as a starting point, and eventually leads were evolved to the resultant chlorobiphenyl-modified lipoglycopeptide that is oritavancin."

Pace, page 970, col. 2 (emphasis added).

Also, specifically regarding Applicants elected species, Li (Li *et al.*, *Curr. Pharm. Design 11*:3111-3124 (**2005**)) teaches how the vancomycin compounds have distinctly unique properties:

> "Based on the above mechanism, several research groups have devised different approaches that circumvent the low affinity bindings between vancomycin and D-Ala-D-Lac. Kahne et al. synthesized modified carbohydrates that are analogs of the aminoglycoside part of the vancomycin. These compounds exhibited good activity against vancomycin resistant microorganisms. ***They suggested that these carbohydrate derivatives function by a different mechanism, in which the modified carbohydrates interact directly with bacterial proteins involved in the transglycosylation step of the cell wall biosynthesis and do not require the binding of terminal peptides for activity*** [30]. Later, they used these sets of small molecules to discover the genes that help to regulate the transglycosylation step of peptidoglycan synthesis and established a genetic basis for activity differences between their compounds and vancomycin [31]."

Li, pages 3112 to 3113 (emphasis added).

In addition to the structure-activity relationships required, Applicants have not reasonably presented the appropriate synthetic chemistries beyond the above identified scope. Accordingly, one of ordinary skill in the art would not be able to make and use the full scope of the claimed compounds.

The amount of direction/working examples

The specification only provides guidance and examples directed to the making and use (e.g. antibiotic) of vancomycin glucose C6 substituted derivatives of the claims which share a common structure which is not representative of the scope of claimed glycopeptides.

Quantity of Experimentation

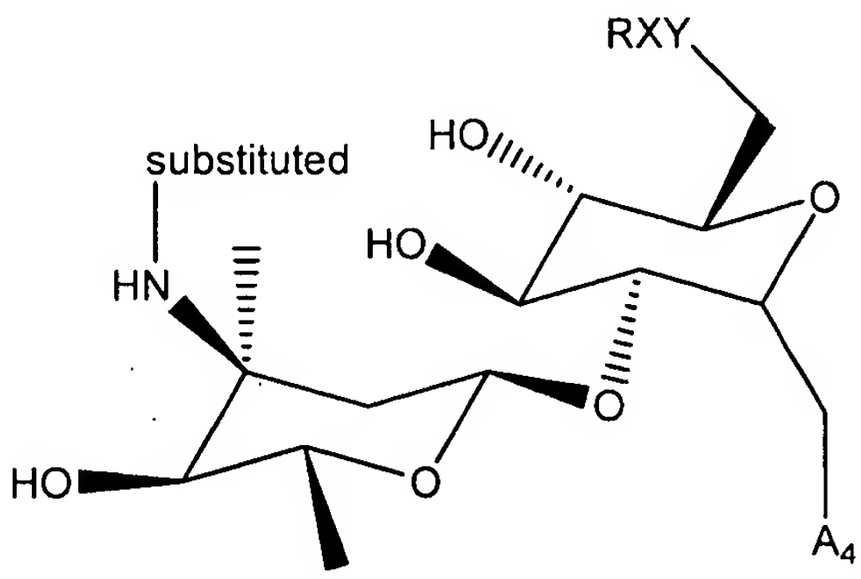
In light of the unpredictability surrounding the making and use of glycopeptide derivatives of diverse structure which possess antibiotic activity, the undue breadth of the

claimed invention, the lack of adequate guidance regarding the making and antibiotic testing of a representative sample of glycopeptides, the lack of exemplified compounds bearing reasonable art-accepted substituents, the lack of critical/essential core structure, one wishing to practice the presently claimed invitation would be unable to do so without engaging in undue experimentation.

Claim Rejections - 35 USC § 112, first paragraph (Written Description)

The rejection of claims 1, 5, 6, 26, 27, 102, 103, 105-107 and 116, under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained.

While Applicants have demonstrated written support for some of the claim breadth, Applicants have not demonstrated support for the full claim breadth. The breadth of potential glycopeptides of different chemical structure as encompassed by claims 1 and 102 is unsupported in light of the failure to substantially teach compounds as broadly as claimed. Specifically, although Applicants have shown support for the heptapeptide structure of naturally occurring vancomycin, Applicants have not shown support beyond the disaccharide structural feature of the following formula:



wherein A_4 is the attachment site of the disaccharide for naturally occurring vancomycin, and Y is directly attached to the C6.

For example, on pages 970-972, Pace (Pace *et al.*, *Biochemcial Pharmacology 71*:968-980 (**2006**)) shows how even the smaller class of vancomycin compounds have unpredictable activities, let alone the largely diverse claimed core by Applicants:

> "The goal of the project that culminated in the discovery of oritavancin was to improve over vancomycin's pharmacokinetic properties, and was based on an understanding of the relevant structure–activity relationship differences between vancomycin and teicoplanin. ***Improvements in alkylated and acylated analogs of vancomycin were deemed inadequate***, and other natural product glycopeptides were subsequently evaluated as platforms [108–111]. Compounds like chloroeremomycin (LY264826) exhibiting better activity and spectrum were utilized as a starting point, and eventually leads were evolved to the resultant chlorobiphenyl-modified lipoglycopeptide that is oritavancin."

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Also, specifically regarding this compound class and Applicants elected species, Li (Li *et al.*, *Curr. Pharm. Design 11*:3111-3124 (**2005**)) teaches how these vancomycin compounds have distinctly unique properties:

> "Based on the above mechanism, several research groups have devised different approaches that circumvent the low affinity bindings between vancomycin and D-Ala-D-Lac. Kahne et al. synthesized modified carbohydrates that are analogs of the aminoglycoside part of the vancomycin. These compounds exhibited good activity against vancomycin resistant microorganisms. ***They suggested that these carbohydrate derivatives function by a different mechanism, in which the modified carbohydrates interact directly with bacterial proteins involved in the transglycosylation step of the cell wall biosynthesis and do not require the binding of terminal peptides for activity*** [30]. Later, they used these sets of small molecules to discover the genes that help to regulate the transglycosylation step of peptidoglycan synthesis and established a genetic basis for activity differences between their compounds and vancomycin [31]."

Li, pages 3112 to 3113 (emphasis added).

Accordingly, one of ordinary skill in the art would not accept Applicants claimed genus as being supported by the instant disclosure. The rejection is maintained.

Claims 1, 5, 6, 26, 27, 102, 103, 105-107 and 116, under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for introducing new matter.

Specifically, in claim 1, Applicants have amended the previous phrase "provided that at least one of the substituents of the formula YXR is not hydroxyl" to recite singular "substituent".

Correction to "substituents" is required because Applicants do not have support to exclude the entire group of YXR being hydroxyl. Applicants original disclosure clearly stated that "at least one of the substituents" meaning any one of the three substituents Y, X *or* R. The same correction is required for claim 102. Claim 103 similarly introduces the same new matter by reciting that –YXR is not hydroxyl.

Further, the correct phrase in each of claims 1 and 102 is "if two or more of said substituents are present". Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1, 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Nicas *et al.*, *Antimicrobial Agents and Chemotherapy 33(9)*:1477-1481 (**1989**).

As in claim 1, Nicas teaches a compound having the vancomycin core, with a modified N-substituted aminohexose (see Figure 1 and Table 1 on page 1478). The substituted C6 meets the criteria of the definition for –YXR, wherein Y = direct bond; X = O; and R = H. None of Y, X or R are individually –OH, as required by the proviso ("provided that at least one of the substituents of the formula YXR is not hydroxyl"). Nicas' compounds also meet the limitations of claim 5 (Y is a direct bond and X is O).

Conclusions

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL

MARK L. SHIBUYA
PRIMARY EXAMINER